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The European Vasculitis Society 2016 Meeting Report

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The 2016 European Vasculitis Society (EUVAS) meeting, held in Leiden, the Netherlands, was centered around phenotypic subtyping in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV). There were parallel meetings of the EUVAS petals, which here report on disease assessment; database; and long-term follow-up, registries, genetics, histology, biomarker studies, and clinical trials. Studies currently conducted will improve our ability to discriminate between different forms of vasculitis. In a project that involves the 10-year follow-up of AAV patients, we are working on retrieving data on patient and renal survival, relapse rate, the cumulative incidence of malignancies, and comorbidities. Across Europe, several vasculitis registries were developed covering over 10,000 registered patients. In the near future, these registries will facilitate clinical research in AAV on a scale hitherto unknown. Current studies on the genetic background of AAV will explore the potential prognostic significance of genetic markers and further refine genetic associations with distinct disease subsets. The histopathological classification of ANCA-associated glomerulonephritis is currently evaluated in light of data coming out of a large international validation study. In our continuous search for biomarkers to predict clinical outcome, promising new markers are important subjects of current research. Over the last 2 decades, a host of clinical trials have provided evidence for refinement of therapeutic regimens. We give an overview of clinical trials currently under development, and consider refractory vasculitis in detail. The goal of EUVAS is to stimulate ongoing research in clinical, serological, and histological management and techniques for patients with systemic vasculitis, with an outlook on the applicability for clinical trials.

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In June 2016, a meeting of the European Vasculitis Society (EUVAS) was held in Leiden, the Netherlands. For the first time, the meeting was structured around parallel meetings of the EUVAS petals as part of the EUVAS Research Council, which was formed in 2011 to enhance scientific research in systemic vasculitis. The petals consist of the following fields of interest: disease assessment, biomarker studies, epidemiology and etiology, clinical trials, registries, genetics, toxicity and infection, database, and histology (Figure 1). The theme of the

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Figure 1. European Vasculitis Society (EUVAS) petals. Fields of interest in systemic vasculitis: disease assessment, biomarker studies, epidemiology and etiology, clinical trials, registries, genetics, toxicity and infection, database, and histology.

meeting was phenotypic subtyping. In this report, we give an overview of the state-of-the art issues arising from the petal meetings. The goal of EUVAS is to stimulate ongoing research in clinical, serological, and histological management, and techniques for patients with systemic vasculitis, with an outlook on the applicability for clinical trials.

Disease Assessment

The careful definition and classification of different forms of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) requires consideration of clinical, serological, and histological evidence. There is considerable overlap among the disease entities. A major study is underway to improve our ability to discriminate among different forms of vasculitis by using data from >5000 individuals with different forms of vasculitis or disease mimics. The diagnostic and classification study in vasculitis (DCVAS)[1] will report preliminary criteria for ANCA vasculitis in the near future. These criteria will assist in separating granulomatosis with polyangiitis (GPA) from microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and other forms of less well-defined vasculitis (which may or may not have ANCA present). The emphasis for the DCVAS project is on characterizing patients for future clinical and epidemiological studies.

Further phenotypic characterization of disease severity is facilitated by using clinical evaluation tools such as the Birmingham Vasculitis Activity Score (BVAS)[2–4] and the Vasculitis Damage Index (VDI).[5,6] These clinical tools are increasingly important in characterizing disease status in terms of activity and damage; this facilitates the distinction among different diseases states. Terms such as active disease, response to therapy, partial response to therapy, relapse, or low-grade disease activity can be defined on the basis of the BVAS assessment. This has already been applied to clinical studies for defining patients with active disease who are eligible for inclusion in studies and in defining a response to the therapy, remission, and relapse. BVAS and VDI also allow more detailed phenotyping of patients with more or less severe end-organ involvement within individual diagnoses (e.g., patients with GPA may have relatively limited disease, whereas other patients with GPA may have much more extensive disease). Defining organ involvement dictates the need for treatment, but may also be a reflection of the underlying pathophysiology and genetic predisposition to severity, as well as susceptibility to disease. Once the classification criteria are established, we need to use them in combination with disease evaluation tools to explore how the different phenotypes behave and respond to therapy, and also to discover whether the phenotypic characterization corresponds to better understanding of underlying pathophysiology.

Database and Long-term Follow-up

The survival of patients with AAV improved dramatically after the introduction of corticosteroids and cyclophosphamide (CYP) in the 1970s.[7] After this, treatment modalities improved with greater safety and outcome. Since the 1990s, EUVAS has designed and accomplished several prospective randomized clinical trials (RCTs), mostly without pharmaceutical companies. The first 4 RCTs revealed new information on how to best treat patients with AAV, according to disease extension and severity.[8–11] However, because AAV is chronic (i.e., relapsing) in at least 50% of patients, it is difficult to draw firm conclusions solely from the results of an RCT that lasts 18 months. Thus, we performed a 5-year follow-up of patients in the first 4 RCTs, and several reports were published from these studies.[12] We obtained more robust information on actual patient and kidney survival, complications due to treatment, and complications due to disease. The longer term follow-up revealed that the initial results were not always robust in the longer term. For example, patients with proteinase 3 (PR3)-AAV appeared to be more prone to relapse if they received pulse CYP compared with continuous oral CYP.[13] Patients treated with methotrexate as induction therapy in the NORAM (Nonrenal Wegener's Granulomatosis Treated Alternatively with Methotrexate) study, most of whom had PR3-ANCA, were exposed to more CYP and corticosteroids in the 5-year follow-up than those who had received CYP as induction. In the short-term perspective, it seems that relapses may not be harmful with regard to the long-term outcome of renal function. However, this may not be true for the longer term perspective. From the 5-year follow-up, we learned that the incidence of malignancies was not higher in this population compared with a matched background population, with the exception of nonmelanoma skin cancer.[14] If this finding reflects an improvement in the treatment strategies, or is a result of a too short a follow-up, we can only tell if the study period is prolonged. Thus, we aimed for a longer follow-up of patients who participated not only in the first 4 RCTs, but also those included in the later IMPROVE (International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides) and RITUXVAS (Rituximab versus Cyclophosphamide in ANCA-associated renal Vasculitis) studies. We would then have a cohort that consisted of approximately 700 European patients followed-up for at least 10 years. The 10-year follow-up has been launched, and we are working on retrieving data on patient and renal survival, relapse rate, cumulative incidence of malignancies, and possibly comorbidities. A larger cohort of patients makes it possible to try to place patients into subgroups with similar clinical presentations and/or phenotypes, in an attempt to identify those with a particular high risk for poor outcome, as Mahr *et al.* did in a cluster analysis.[15]

Registries

Patient registries and databases play an important role in clinical research, patient care, and healthcare planning. The increasing clinical trial activity in the field of vasculitis, the need to collect long-term data on biologic treatment safety and efficacy in routine care, and the wide variety of clinical manifestations in this group of rare diseases, has led to the development of several vasculitis registries across Europe. Eight European countries have already established such registries (Czech Republic, France, Ireland, Norway, Poland, Portugal, Spain, and the United Kingdom[15−23]). In many other countries, this topic is on their research and clinical agendas (e.g., Germany, Switzerland, and the Netherlands). Most of the existing vasculitis registries are currently designed solely for research purposes (e.g., UKIVAS [UK and Ireland Vasculitis Rare Disease Working Group]), whereas others are also being used as electronic medical records in daily practice (e.g., rheumatoid patient/vasculitis). The registries are at different stages of development: the Polish Vasculitis Registry and UKIVAS have not yet initiated collection of follow-up and outcome data; the Czech Registry has prospective follow-up of 25% of patients; and the other registries have prospective data on most registered patients. Different medical and surgical specialties have been contributing to data collection (nephrology, rheumatology, internal medicine, immunology, and pediatrics), which strongly influences the case mix, and in some countries, such as Spain, there is >1 vasculitis registry depending on the medical speciality or geographic region. The type and detail of information recorded is slightly different in each country, with most of the variation occurring in registries created for patients under the care of nephrology or rheumatology physicians. Table 1 summarizes the information captured in the most representative vasculitis registries of each country.

Overall, there are approximately 11,000 patients registered across Europe, with the FVSG (French Vasculitis Study Group) registry and UKIVAS being the largest, and most recruits have AAV, which is partially explained by the high proportion of recruiting renal centers. Portugal and Poland have developed vasculitis registries relatively recently, basing their data sets on adaptations of other preexisting European registries, as part of the EUVAS collaborative network. However, there remains a critical need to define a core set of agreed upon data items to carefully balance granularity and feasibility of data collection. It is envisaged that this will represent a core EUVAS data set that all newly developing EUVAS-aligned registries will adhere to.[24,25] This will facilitate the ultimate goal of distributed analysis of research and clinical questions across the entirety of European vasculitis recruits, the greatest current barrier to which is a lack of commonly agreed upon terminology related to elements as simple as the name given to a particular vasculitis syndrome. The data dictionaries for existing registry initiatives will be stored in a cloud-based resource, accessible to all current and prospective registries.

An important consideration when seeking to analyze clinical data from diverse European sources is the associated data privacy and ethical issues related to data sharing. It is for this reason, and because of the prohibitive cost of a central EUVAS registry portal, the society has decided to proceed on the basis of distributed analysis of aggregated data from each registry. Using this approach, which relies completely on alignment of data dictionaries, analysis code related to a specific question is run separately within each registry, and the summary data are returned centrally for collation. For this purpose, EUVAS has adopted the long-term strategy of developing an informatics hub

Table 1. Currently active European vasculitis registries

Registry details	Czech Republic	France	Ireland and the UK	Norway	Poland	Portugal	Spain
Name of the registry	Czech Registry of AAV	FVSG Registry	UKIVAS	NorVas	Polish Vasculitis Registry	Reuma.pt / Vasculitis	REVAS
Start date	2009	1981	2010	2014	2015	2014	1990
Type of vasculitis	AAV (to be extended)	All	All	All	All	All	All
Patients (*n*)	850	3304	3710	399	650	574	1650
Centres (*n*)	16	101	51	8	13	9	25
Medical specialties	Various	Various	Various	Rheumatology (nephrology invited)	Various	Rheumatology	Internal medicine
Adapted for routine care	No	Yes (recent)	No	Yes	No	Yes	No
Features captured demographics	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Classification/diagnosis	EMA	CHCC	CHCC	CHCC and ACR	CHCC	CHCC and ACR	CHCC
Clinical features	Yes	Yes	Yes	No (BVAS)	Yes	Yes	Yes
BVAS	Yes	Yes	Yes	Yes	Yes	Yes	Yes
VDI	Yes	Yes	Yes	Yes	Yes	Yes	Yes
FFS	No	Yes	No	No	No	Yes	Yes
Laboratory	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Biopsy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Adverse events	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Deaths	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Informed consent	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Funding	Public/industry	Public	Public	Public	Public/industry	Industry	—
Biosampling	Yes	Yes	Yes	Yes (to be started)	Yes	Yes	No

AAV, antineutrophil cytoplasmic antibody (ANCA)−associated vasculitis; ACR, American College of Rheumatology; BVAS, Birmingham Vasculitis Activity Score; CHCC, Chapel Hill Consensus Conference; EMA, European Medicines Agency; FFS, Five factor score; FVSG, French Vasculitis Study Group; ICD, International Classification of Diseases; NorVas, Norwegian Vasculitis & Biobank Registry; REVAS, "Registro Español de Vasculitis Sistemicas," Spanish Registry of systemic vasculitides; UKIVAS, UK and Ireland Vasculitis Registry; VDI, Vasculitis Damage Index.

that will design and administer these distributed analyses. This will allow us to address important research questions and to benchmark key performance indicators included in the agreed core-set items across European countries. It will provide robust data on long-term outcomes in vasculitis, and allow for better service planning and commissioning (particularly of expensive biologic agents). This capability is a core requirement of the current European Reference Network initiative, and the existing strength within the EUVAS community has enabled alignment with pediatric rheumatology, immunodeficiency, and autoinflammation groups across Europe to form a new umbrella network to improve care for patients with these rare diseases.

Genetics

The different clinical and laboratory features of the diseases grouped under the umbrella of AAV have generated considerable interest in the investigation of the factors that contribute to such phenotypic differentiation. Genetic studies have often tried to clarify the basis of this clinical heterogeneity. AAVs are rare diseases, have little familial aggregation, and mouse models of myeloperoxidase (MPO)-ANCA and PR3-ANCA vasculitis only partially recapitulate the phenotype of these conditions. Therefore, case−control genetic association studies are considered to be the most feasible approach to investigate the genetic background of AAV.[26]

Several studies that focused on candidate genes were performed over the past few decades, but they were often limited by small sample sizes, and their results were difficult to replicate in different populations. Nevertheless, they provided early evidence of a predisposing role of genetic variants within human leukocyte antigen (HLA) class II, *SERPINA1* (encoding α1-antitrypsin), and other autoimmunity genes (e.g., *PTPN22*),[27−29] but they were unable to detect distinct genetic associations of the different AAV forms. A major breakthrough in AAV genetics came from 2 genome-wide association studies: 1 was developed in Europe by the European Vasculitis Genetics Consortium (EVGC) and included both GPA and MPA[30]; the other was performed in the United States and only included GPA patients.[31] Both studies revealed strong genetic associations between GPA and the HLA-DP region, but the European study also identified distinct genetic associations between GPA and MPA. GPA was found to be associated not only with HLA-DP but also with polymorphisms of the PRTN3 and SERPINA1 genes, whereas MPA was associated with HLA-DQ. Notably, the genetic associations were stronger with ANCA specificities (i.e., PR3-ANCA−positive patients vs. MPO-ANCA−positive patients) than with the clinical syndromes (GPA vs.

MPA). This study was the first to demonstrate a clearly different genetic background between AAV forms, leading to the provocative proposal of a new classification of AAV into PR3-positive and MPO-positive polyangiitis.[30] This study also underlined the pathogenic importance of PR3 in GPA because of the association between this condition and variants of the genes encoding PR3 and 1 of its major inhibitors, α1-antitrypsin.

A recent meta-analysis confirmed the results of the genome-wide association studies and extended the spectrum of the AAV-associated variants to other genes commonly involved in autoimmune diseases, such as CTLA-4, FCGR2A, and PTPN22. This study further confirmed that genetic associations were stronger with ANCA subtypes than with the clinical diagnosis; it also showed significant associations of the same polymorphisms in opposite directions in GPA versus MPA, as well as in PR3-ANCA−positive subgroups versus MPO-ANCA−positive subgroups.[32]

Genetic studies in EGPA are scarce and involve small cohorts. However, an association with HLA-DRB4 has been detected in independent cohorts,[33,34] and larger studies are awaited to clarify whether the association lies in this locus or in nearby HLA regions.

Genetic variants may also be shared as predisposing factors by the different AAV forms; this is the case not only of single nucleotide polymorphisms but also of gene copy number variations (CNVs); for example, FcGR3B gene CNVs, which are linked to several autoimmune disorders, have been associated with EGPA in a recent study[35] and also with GPA and MPA in an earlier study.[36] These and other variants may constitute a common genetic background for AAV.

Current and future studies in AAV will be directed not only to further refine the genetic associations with distinct disease forms or disease subsets, but will also try to explore the potential prognostic significance of genetic markers. In addition, the results of pharmacogenetic investigations are becoming available and will probably allow better profiling of the response to immunosuppressive drugs such as CYP and rituximab (RTX).[37,38]

Histology

Renal histopathological features vary widely among patients with AAV, from mild focal segmental extracapillary proliferation to diffuse crescentic necrotizing glomerulonephritis (GN) with granulomas and tubular intra-epithelial infiltrates. Moreover, some patients have nearly no abnormalities on renal biopsy, whereas others have extensive glomerulosclerosis. Categorization based on ANCA serotype shows that MPO-positive patients have more chronic and active lesions compared with PR3-positive patients.[39] This fits well with the growing evidence from genetic studies for pathophysiological differences between MPO- and PR3-AAV, which showed associations between polymorphisms in the MHC genes and PR3-or MPO-positivity.[32] Genetic associations with clinical diagnosis are much weaker, which favors the idea of classifying patients according to ANCA serotype. Studies on prognostic markers yielded conflicting results regarding PR3 and MPO positivity, therefore limiting their predictive value.[40] In contrast, histopathological parameters, such as percentage of normal glomeruli and amount of fibrinoid necrosis, have been identified as strong predictors for renal function during follow-up.[41] To summarize histopathological features in ANCA-associated GN (AAGN), a histopathological classification was launched in 2010.[42] The classification distinguishes focal, crescentic, mixed and sclerotic class, and correlates with long-term renal outcome. The classification has been validated in >13 studies, which have noted some discrepancies between crescentic and mixed class.[43] A large international validation study is currently underway to solve these controversies and improve the prognostic value of the classification system. It remains unknown whether the histopathological classes have distinct genetic backgrounds. A study that used a mouse model for AAGN pointed toward this possibility, showing that the genetic makeup determined the percentage of crescentic glomeruli.[44] Ultimately, an approach in which histology is incorporated in guidance of treatment should be investigated.

Biomarker Studies

After >30 years, ANCAs are still the most clinically valuable biomarkers in vasculitis. The need for standardization of ANCA assays brought investigators together, which eventually led to the foundation of EUVAS.[45] The next step after standardization was to agree on how the different assays should be used. A consensus agreement was reached, which had an immense impact on laboratory practices for many years.[46] In short, the consensus statement stipulated that all samples referred to a clinical immunology laboratory with a request for ANCA testing should be subjected to an indirect immunofluorescence assay using ethanol-fixed human neutrophils as the substrate. In cases of positive results, the specificity of the autoantibodies should be determined using antigen-specific immunoassays such as the enzyme-linked immunosorbent assay for MPO-ANCA and PR3-ANCA. This consensus statement was based on expert opinion and not on any specific study. The notion that indirect immunofluorescence was the most sensitive method for the detection of pauci-immune vasculitis was challenged in studies that used capture enzyme-linked immunosorbent assays with carefully selected capturing antibodies.[47]

From the beginning, when EUVAS started to perform prospective clinical studies, it was decided that samples should be collected for future biomarker studies. The samples are stored in a central serum bank, which for many years was located at Statens Serum Institut in Copenhagen, Denmark. It has recently been moved to Lund, Sweden. The samples have been used for studies that evaluated new potential biomarkers.[48] In our continuous search for biomarkers to predict clinical outcome, promising new markers such as antiplasminogen antibodies and antimoesin antibodies will be the subject of future research. Traditionally, the focus has been on ANCA testing.[49] EUVAS has recently launched studies focusing on the evaluation of automated studies.[50] This was a major topic at the Leiden meeting. The main conclusion of these studies was that automated platforms and modern solid phase immunoassays are superior with respect to diagnostic yield to the standard indirect immunofluorescence on ethanol-fixed neutrophils. Consequently, there is now an urgent need to update the consensus statement from 1999; this is a work that is now in progress.

Clinical Trials

Over the last 2 decades the European study group, the French Vasculitis group, and the American VCRC (Vasculitis Clinical Research Consortium) have completed a host of clinical trials that have provided the evidence base to allow refinement of therapeutic regimens in the treatment of AAVs; these trials have demonstrated an equivalence or improvement following reduced duration of CYP treatment, adjunctive use of plasmapheresis, and substitution of methotrexate or mycophenolate mofetil for CYP. Although definitions of remission in these studies have varied somewhat, the overall rates of remission induction have generally been high (80%−90%; see Table 2), meaning that for most patients, these regimens are successfully turning the disease off. However, 2 major problems remain with these treatment strategies: the issue of disease relapse and adverse events. Newer trials have specifically been developed to address the issue of relapse, with regard to duration and type of immunosuppressive treatment, which will better inform us of what long-term treatment strategy is needed. Despite complete avoidance or significant reduction in CYP dosages, adverse events, and specifically infectious complications, have remained equal in various treatment arms. There is a consensus that some of these adverse events have contributed to the use of high-dose oral and i.v. glucocorticoids (GCs), which have been mandated and have been a mainstay in all of the clinical trials to date. GC dosing in ANCA vasculitis and other inflammatory diseases has never really been subjected to thorough investigation, but the PEXIVAS (Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis) study, which should report in 2018, has investigated 2 different prednisolone induction regimens. However, even PEXIVAS has mandated pulsed methylprednisolone use, and one question is whether more extreme steroid minimization is possible. In the world of transplantation, this has been achieved by using potent induction therapies that allow steroids to be withdrawn after 1 or 2 weeks. In AAV, steroid minimization has been achieved in small cohorts and randomized studies using combination induction therapies (combining low-dose CYP and RTX)[51,52] or using alternative steroid-sparing agents such as avacopan, which is a C5a receptor inhibitor.[53] The results are so far encouraging, and cohort studies from 2 London units have suggested equivalent remission rates and better side effect profiles, with lower rates of new-onset diabetes and fewer infections. Similarly, a phase II clinical trial of avacopan suggested equivalent outcomes to traditional steroid-based induction therapies. Both strategies now require testing in larger phase III studies, and although the ADVOCATE (C5a Receptor Inhibitor in AAV) trial of avacopan induction is currently underway, steroid-free induction therapy with RTX- and CYP-based combination treatment is yet to begin. However, these and other future trials should allow us to try to maintain efficacy but drive down side effect rates, thus improving outcomes for our patients. Several clinical trials are currently under development.

Table 2. Induction remission trials in antineutrophil cytoplasmic antibody−associated vasculitis

Trial	Compared	Results	Rates
CYCAZAREM	CYP vs. CYP/AZA	Equal remission	93%
NORAM	MTX vs. CYP	Equal remission	89% vs. 90%
CYCLOPS	i.v. vs. oral CYP	Equal remission	88.1% vs. 87.7%
RAVE	RTX vs. CYP	Equal remission: better response in relapsers and PR3-with RTX	64% vs. 53% (off steroids by 6 mo) 72% vs 42% in relapsers
RITUXIVAS	RTX/CYP vs. CYP/AZA	Equal remission	76 vs. 82%
MYCYC	MMF vs. CYP	Equal remission but may need more steroids	73% vs. 74% 90% vs. 88% with more steroids

AZA, azathioprine; CYCAZAREM, cyclophosphamide vs. azathioprine for early remission phase of vasculitis; CYP, cyclophosphamide; CYCLOPS, randomized trial of daily oral versus pulse cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; MYCYC, clinical trial of mycophenolate versus cyclophosphamide; NORAM, nonrenal Wegener's granulomatosis treated alternatively with methotrexate; RAVE, rituximab for ANCA-associated vasculitis; RITUXVAS, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine regimen; RTX, rituximab.

GOOD-IDES (Open-Label Phase II Study to Evaluate the Efficacy and Safety of IdeS in Anti-GBM Disease): Antibody Removal by IdeS Protein in Anti-GBM Disease

IdeS (IgG-degrading enzyme of *Streptococcus pyogenes*) is an enzyme produced by Streptococci that has a remarkable specificity for IgG. Phase I studies have shown that a single infusion of IdeS in a dose of 0.125 mg/kg can degrade all circulating IgG in the body to fc- and fab-fragments within a few hours. In addition, animal experiments have shown that IdeS *in vivo* is able to cleave the fc-fragments of anti–glomerular basement membrane (GBM) antibodies bound in the kidneys.[54] Anti-GBM disease is a rare form of immune-mediated small vessel vasculitis. The pathogenesis is driven by autoantibodies directed to discrete epitopes on the α-3 chain of type IV collagen. Most patients present with a severe form of rapidly progressive GN, and in addition, approximately one-half of these patients experience alveolar hemorrhage, which can be life-threatening. We hypothesize that a single infusion of IdeS in addition to standard care will provide better renal survival compared with historical controls. Fifteen patients with anti-GBM who have a bad renal prognosis will be studied in an open-label, nonrandomized multicenter trial. This study will include patients with anti-GBM disease with circulating levels of anti-GBM and a glomerular filtration rate (GFR) of <15 ml/min or a GFR that is declining despite standard care. Patients with anuria lasting >48 hours, or who are on dialysis and required ≥3 dialysis sessions will also be included. Patients with ongoing infection or other severe comorbidities will be excluded. All patients will receive a single infusion of 20 mg of IdeS and IV or oral CYP. Plasma exchange will be given to keep anti-GBM levels below toxic levels according to local practice. Steroids will be given as i.v. bolus doses the first 3 days of treatment and as oral prednisolone in doses equivalent to other EUVAS studies. The main endpoint is the proportion of patients with independent renal function at 6 months. Secondary endpoints include changes in GFR, albuminuria. and safety parameters. Coordinators are Professor Mårten Segelmark, Linköping University, Sweden, with financial support given by Hansa Medical AB, Lund, Sweden. Four centers in Sweden, 2 in Denmark, 4 in England, 1 in the Czech Republic, and 2 in France have been accepted as the centers for the study; more centers may be included.

HAVEN: Hydroxychloroquine in GPA

We propose a phase II double-blind, randomized placebo-controlled trial, HAVEN (Hydroxychloroquine in ANCA Vasculitis Evaluation), in adult patients with mild to moderate AAV who continue to have active disease after immunosuppressive induction therapy. Seventy-six patients will be randomized to hydroxychloroquine (HCQ) or placebo in a 1:1 ratio, in addition to standard maintenance therapies: GCs + azathioprine and/or methotrexate, and/or mycophenolate, and/or previous RTX >6 months ago. The primary endpoint assessed at 52 weeks will be the percentage of patients with uncontrolled AAV (defined as BVAS >3) treated with adjunctive HCQ 400 mg/d versus placebo. Secondary outcomes will include complete remission (BVAS = 0) and flare rates, time to remission, cumulative GC dosage, damage scores, adverse events, lipids, quality of life, and fatigue. Study duration is 4 years. We aim to demonstrate that repurposing HCQ in AAV improves vasculitis activity, morbidity, and quality of life. Coordinators are David D'Cruz and Alina Casian, Guy's Hospital, London (now funded by the Medical Research Council, London, United Kingdom).

SMARTVAS: Rituximab/Cyclophosphamide and Minimal Dose Glucocorticoid in AAV

Patients with AAV are highly susceptible to therapy-related adverse effects. Attempts to reduce these have so far failed, likely due to high GC dosing. We have successfully piloted a GC avoidance regimen and propose to compare this against conventional therapy to test whether it maintains efficacy while reducing adverse events, improves patient health, decreases costs, and reduces hospitalizations. In SMARTVAS (steroid avoidance trial in AAV), we will gain mechanistic insights into biomarkers of disease activity by comparing traditional urinary blood and protein with novel biomarkers including MCP-1 and CD163. The randomized controlled trial uses a 2 × 2 factorial design, randomizing patients to CYP or low-dose CYP with RTX, combined with either 2 weeks of prednisolone (Pred) or 6 months Pred taper. This will be carried out in tertiary AAV centers, and will include patients with newly diagnosed AAV (GPA or MPA), who are ANCA positive and have biopsy proven vasculitis or evidence of pulmonary hemorrhage. We will include patients of all ages and levels of renal function. We will exclude: relapsing patients; patients who have been administered >2 weeks of oral GC or >1 g of methylprednisolone before randomization; patients with hepatitis C or B virus, or HIV infection; patients with malignancy within 5 years, except nonmelanoma skin cancer; patients who are pregnant or breast feeding; and patients who have been dialysis dependent for >14 days. The experimental arm will consist of induction with RTX 2× 1 g given 2 weeks apart, with methylprednisolone 250 mg IV, and CYP 500 mg IV every 2 weeks (dose adjusted for age) and oral Pred 60 mg/d for 1 week and 30 mg/d for the next week. The standard arm will consist of CYP adjusted for weight, age, and renal function (range: 7.5−15 mg/kg) given in 6 to 10 doses at 2 to 3 weekly intervals and Pred, starting at 1 mg/kg daily (maximum: 60 mg/d) tapered as guided by PEXIVAS results. After induction, all patients will commence azathioprine. The primary endpoint will be full disease remission at 6 months, defined by a BVAS of zero, with adherence to GC protocol. Secondary endpoints will be adverse effects, incidence of new-onset diabetes, estimated GFR, weight gain, and quality-of-life assessments, all at 6 months, and actuarial time to remission. In addition to clinical outcomes, we will perform a health economic analysis to investigate the within-trial and long-term incremental cost effectiveness of GC-free maintenance therapy in AAV. The analysis will use quality-adjusted life years, in line with NICE (National Institute for Clinical Excellence) guidance.[19,20] We have estimated sample size based on remission rates of 75% from recent clinical trials (RITUXVAS [rituximab versus cyclophosphamide in AAV], RAVE [rituximab for AAV], and MYCYC [mycophenolate mofetil versus cyclophosphamide for remission induction in AAV]). For noninferiority between the standard and experimental arms, 262 patients are required for 80% power (95% 2-sided confidence interval) to exclude a difference in remission of >15%, an acceptable margin if there are significant reductions in adverse events. Assuming a 10% dropout rate, we need to recruit 292 patients. Based on a survey sent to 30 UK vasculitis centers, which all support this proposal, we estimate 3 patients/center per year, which allows total recruitment over 3.5 years, and 4 years to complete follow-up. This proposal is from Alan Salama, University College London, London, United Kingdom.

BIOVAS: Biologic Therapies in Refractory Non-ANCA Vasculitides

Biologic therapies are widely used in autoimmune diseases including AAV. The non-ANCA vasculitides represent several rare and very rare disorders for which there is a strong rationale for the efficacy of biologics but limited evidence for their use. BIOVAS (biologic agents in non-ANCA vasculitis) will study biologics targeting 3 key pathogenetic pathways across the spectrum of refractory non-AAV. It will recruit the minority of patients in whom adequate disease control fails with conventional therapy. This subgroup has increased risks of vital organ failure and death, and intolerance of conventional agents. They represent patients with the highest need and for whom a cost-effectiveness analysis is likely to be favorable if biologic agents prove clinically effective. The pragmatic, crossover design will optimize the power of the trial and reflect the real-world nature of adult and pediatric vasculitis care. Patients (n = 140) from 8 non-AAV subgroups will be recruited from 15 vasculitis centers in the United Kingdom and Ireland and will be randomized to a sequence of 4 interventions (3 active and placebo) that will be administered double-blind, in 4-month treatment periods. Responders will continue the effective intervention to relapse or trial end at 24 months, whereas nonresponders will move to the next intervention in the sequence. BIOVAS aims to deliver a data set that will clearly guide funding decisions and National Health Service policy development in vasculitis of benefit both to vasculitis patients and their families, and to society at large. This study is proposed by David Jayne and Seerupani Gopulani, Cambridge, United Kingdom.

Immunomonitoring in Rituximab-Treated AAV Patients

RTX, a chimeric CD20 antibody was successfully applied as induction treatment in AAV.[55,56] Despite successful induction therapy, a subset of patients relapsed while they were being treated with azathioprine, methotrexate, or mycophenolate mofetil as a maintenance regime.[57−59] Relapses of AAV can be severe, resulting in organ damage or death.[12] In addition, the adverse effects of these immunosuppressive therapies have a high morbidity and lead to long-term complications, such as osteoporosis or cardiovascular disease.[60] Therefore, continuous efforts are directed at the development of better maintenance regimens for AAV patients but also at early identification of patients at high risk for relapse.

A recent, pivotal randomized trial (MAINRITSAN [maintenance of remission using rituximab in systemic AAV] study) demonstrated the superiority of RTX over azathioprine as maintenance treatment in AAV.[61] This study confirmed previous observations from several uncontrolled cohort studies that RTX could be used effectively and safely as maintenance treatment in AAV patients (Table 3).[62−72] However, in all the published studies, RTX was used in a different regimen, with different timing and dosing. Roughly, RTX regimens could be classified into 2 different regimens, "fixed" or "on-demand" treatment. Fixed treatment applied RTX with repeated dosing at fixed intervals. On demand treatment applied RTX as a (re-)treatment upon clinical signs of a relapse.[69,71,72] The RTX fixed treatment strategy has been widely used in recent years (Table 3). This strategy has high sustained remission rates of 74% to 100%, with relapse rates varying from 0% to 20% during follow-up periods of 18 to 84 months versus RTX in nonfixed intervals, which have 19% to 56%

Table 3. Studies investigating RTX as maintenance regimen in AAV patients

Trial	Study population	Maintenance regimen	Induction	Follow-up (mo)	Relapse	Safety	Comments
MAINRITSAN Guillevin *et al.*[61]	GPA/MPA/rlAAV 87/23/5 New Dx	RTX 500 mg, day 0,14; then 6 mo (3×) $n = 57$ Daily azathioprine till month 22. $n = 58$	Cyc + GC 6 mo	28	5% 29%	Similar AE in both groups (25%)	
Pendergraft *et al.*[62]	GPA (43%)/MPA Rec/Ref and new Dx ($n = 172$)	1 g every 4 mo	CYC or RTX	84	20% (severe relapses 5%) Average in remission: 2.1 yrs	14% severe infections (36% pulmonary)	
Rhee *et al.*[63]	GPA/MPA Rec/ref $n = 39$	1 g every 4 mo for 2 yr	Cyc or RTX	12 ($n = 39$) 24 ($n = 20$)	7.6% Relapse rate: 5.0/100 patient-years	5% severe AE	Decrease of 87% in 30% of patients with IS
Smith *et al.*[64]	GPA/MPA Rec/Ref $n = 73$	1 g every 6 mo × 2 yr ($n = 45$) vs. RTX only in relapses (n = 28) Cumulative dose in patients treated regularly: 6 (2–11) g	Multiple, including biologic	55 (19–62)	12% preventive strategy vs. 72% retreatment upon relapse at 24 mo (26% vs. 81% at 48 mo)	Severe AE 47% RTX vs. 32% non-RTX severe infections 27% vs. 21%	Considerable decrease in GC, 38% discontinue completely IS are discontinued
Roubaud-Baudron *et al.*[65]	GPA (85%)/MPA Rec/Ref (90%) New Dx (10%) ($n = 28$)	375 mg/m^2 every 6 mo ($n = 13$) 1 g biannual ($n = 4$) 1 g every 12 mo ($n = 3$) Other regimens ($n = 8$); average infusions: 4 (2–10)	CYC or RTX or MTX	38 (21–97)	7% Relapse rate: 2.0/100 patient-years	1 severe AE (infection) 3 patients with mild infections	Concomitant use of IS in >50% pt RTX
Charles *et al.*[66]	GPA (88%)/MPA Rec/Ref ($n = 80$)	375 mg/m^2 every 6 mo (26%) 500 mg every 6 mo (14%) 1 g every 6 mo (11%) Others	Multiple, including RTX	18 (12–37)	20% treated with RTX vs. 44% without the drug	22 SAEs 15% inf. 5% patients died	
Alberici *et al.*[67]	GPA (90%)/MPA Rec/Ref (97%) New Dx (3%) ($n = 69$)	1 g every 6 mo 2 yr Cumulative dose: 6 g	CYC or RTX	59 (44.5–73.3)	13% 40% after complete discontinuation of RTX (34 m av CR)	93 SAEs in 36 patients 29% severe infections (57% in resp tract)	90% of the patients are able to dis-continue IS and 48% GC
Calich *et al.*[68]	GPA Rec/Ref (95%) New Dx (5%) ($n = 66$)	500 mg every 6 mo × 1.5 yr Cumulative dose: 4.6 ± 1.7 g	RTX	34.2 (8–60) mo	12%, RR: 11.2 /100 patient-years 5 pts relapsed in the first 2 yrs	21 severe AE. 13.6% infections	50% granulomatous disease Reduction GC
Besada *et al.*[70]	GPA Rec/Ref (80%) New Dx (20%) ($n = 35$)	2× 1 g 2 wk apart, then 2 g annually Cumulative dose: 8 g (2–13 g)	RTX 2× 1 g	47 (2–88) mo	23% Relapse rate: 6.6/100 patient-years	26% severe infections 37% disc RTX (↓IgG)	GC reduced from 22 mg to 5 mg/d 21% disc. compl.
Cartin-Ceba *et al.*[71]	GPA Rec/ref ($N = 53$)	375 mg/m^2/wk × 4 (90%) or 1 g every 2 wks × 2 (10%) upon CD19+cells or increase in PR3-ANCA vs. RTX only in relapses	CYC or RTX	52.8 (32.4–74.4)	0% patients treated according to a preventive strategy vs. 32 on relapse	30 infections (9 in respiratory tract)	
Yusof *et al.*[72]	GPA ($N = 35$)	2× 1 g RTX upon clinical presentation of relapse (BVAS >1)	2× 1 g RTX + GC	18	Naive B cells 6 mo: RR 0%. 12 mo: 14% at 18 mo. No naive B cells 6 mo: 31% and 54%	Not determined	
Moog *et al.*[69]	GPA/MPA ($N = 11$)	375 mg/m^2 every 6–9 mo (53%), relapse (35%) or B cells/ANCA titers (12%) Mean cumlative dose: 1608 mg Mean no. of doses: 2.2	Single RTX 375 mg/m^2	24	4/11 minor relapse in 24 mo	26 infections in 11 patients, correlated with previous CYC	Retrospective

AAV, antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis; AE, adverse event; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; Dx, diagnosis; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; IS, immunosuppression; MAINRITSAN, maintenance of remission using rituximab in systemic AAV; MPA, microscopic polyangiitis; RTX, rituximab; SAE, serious adverse event.

sustained remission with relapse rates of 32% to 72%.[59] There is a risk of overtreatment using the fixed retreatment strategy. In contrast, a major advantage is the successful tapering and even discontinuation of glucocorticoids in patients on a fixed retreatment regimen. The RTX on demand strategy also seems effective in uncontrolled cohort studies[69,71]; however, this treatment strategy inherently holds the risk of serious organ damage and high use of GCs because clinical relapse can have acute onset and progression.

Therefore, there is increasing tendency to apply RTX retreatment on the basis of established biomarkers of AAV disease. However, a rise in ANCA titers or B-cell repopulation does not consistently predict a relapse in AAV.[59] In addition to these different treatment regimens, the approach within each study to use RTX was different. Studies that investigated the fixed treatment strategy used heterogeneous intervals ranging from 4 months,[62,63] to 6 months,[64–69] to annually.[65,70] Although studies that investigated on demand treatment applied RTX as a (re-)treatment at the clinical signs of a relapse,[69,71,72] the definition of relapse, however, was also heterogeneous—either based upon the discretion of the clinician discretion or upon specific biomarkers (e.g., ANCA titer or repopulation of B-cells).[65,71] There is currently an ongoing trial that is investigating these 2 dosing regimens to address these issues (ClinicalTrials.gov NCT01731561). Briefly, patients are receiving retreatment with RTX based on ANCA titers and CD19+ B-cell return or at fixed 6-monthly intervals. Taken all together, one can appreciate that, although effectiveness of RTX is well-documented, these studies failed to elucidate the optimal maintenance strategy for the application of RTX in AAV patients.

Refractory Vasculitis

After >2 decades of collaborative effort, treatment and prognosis of AAV has clearly improved.[73,74] First-wave EUVAS trials constituted a pioneering attempt of personalized medicine by stratifying patients and treatments according to predicted severity. These trials were mainly aimed to more adjusted and standardized use of available immunosuppressive agents (CYP, methotrexate, azathioprine, and later, mycophenolate) in AAV (specifically GPA and MPA) and resulted in an improvement in long-term prognosis. Subsequently, new therapies became available and the efficacy of RTX as the first alternative to CYP for patients with severe disease was demonstrated. Other approaches are currently being tested to improve current induction therapies, including avacopan (C5a inhibitor)[53] or plasma exchange.[75]

Evidence-based recommendations based on clinical trials performed with AAV patients are frequently extrapolated to other forms of severe necrotizing systemic vasculitis. For instance, RTX has also been applied to severe or refractory forms of EGPA,[76] IgA vasculitis,[77] and polyarteritis nodosa.[78] Treatment with RTX has also been a major advance in the treatment of cryoglobulinemic vasculitis; in this case, it was supported by specific clinical trials that demonstrated its efficacy.[79,80]

However, some patients do not appropriately respond to current therapeutic options and are referred to as refractory patients. Refractory patients have been identified in all vasculitis categories. A subset of previously considered refractory AAV patients have subsequently benefited from RTX, particularly patients who failed induction of remission and relapsing patients. RTX has overcome some of side effects of CYP, although symptomatic hypogammaglobulinemia with associated infection may be of concern in some patients after repeated infusions.[81] For relapsing GPA patients with moderate disease, abatacept may also be a promising therapy[82]; it is being tested in a phase III clinical trial. Refractory patients, particularly before the availability of RTX, were treated with a variety of other agents, including, anti-CD52 alemtuzumab,[83] deoxyspergualin (gusperimus),[84] antithymocytic globulin,[85] IV Ig,[86] and, more recently, a combination of RTX with low-dose CYP. Sporadically, some patients have been subjected to autologous stem cell transplantation.

In the field of large-vessel vasculitis, recent clinical trials have demonstrated that relapsing patients with GCA may benefit from anti–interleukin (IL)-6 receptor blockade with tocilizumab[87,88] or from recombinant Ig-CTLA-4 abatacept.[89] Sirukumab (anti–IL-6) is currently being tested in a randomized controlled trial.

The term refractory patients is heterogeneous and includes patients with severe irreversible organ damage at the time of diagnosis, which is difficult to reverse with any immunosuppressive or immunomodulatory treatment, patients with grumbling disease despite treatment, relapsing patients, and patients with intolerance or severe toxicity caused by current treatments. Other categories also need to be considered: heterogeneity and misdiagnosis. Pathogenic heterogeneity within what has been considered a single disease may apply to several systemic forms of vasculitis and may determine why some patients may not respond to commonly useful therapies but may respond to others. A clear example of pathogenetic heterogeneity is polyarteritis nodosa; a similar clinicopathological phenotype may be triggered by viruses (mainly hepatitis B virus), produced by ADA-2 deficiency, associated with hematologic malignancies, or be idiopathic.[90,91]

Another example may be ANCA-positive EGPA, which resembles MPA or GPA more, and ANCA-negative EGPA, which resembles primary hypereosinophilic syndrome and potentially benefits from eosinophil-targeting therapies. In this sense, refractory and/or relapsing EGPA is unique among AAV in responding to mepolizumab.[92] Certain chronic manifestations of EGPA (e.g., asthma) may also respond to anti-IgE omalizumab.[93] Cryoglobulinemic vasculitis may be triggered by viruses, mostly hepatitis C virus, B-cell clones or malignancies, and plasma-cell malignancies or clones (such as monoclonal gammopathy of unknown significance); the latter may not respond to RTX, but it will respond to lenalidomide or botezomib.[94]

Misdiagnosis may also account for refractoriness, and this may particularly apply to patients with large-vessel vasculitis, which is frequently diagnosed on clinical or imaging grounds. When there is an incomplete response, this may also suggest an alternative diagnosis (i.e., structural vasculopathy, periaortitis and/or IgG4 disease, AAV, among others).

The potential therapeutic armamentarium to be tried in patients with truly refractory systemic vasculitis is quickly expanding as new targeted or immunomodulatory therapies have shown efficacy or are considered in other chronic inflammatory diseases. Options for refractory patients may include extending therapies that have been effective in some systemic vasculitis to other vasculitis types with common pathogenic mechanisms (i.e., avacopan tested in AAV to IgA vasculitis or cryoglobulinemic vasculitis; tocilizumab effective in GCA to AAV) or applying targeted therapies that have been proven useful in other autoimmune or chronic inflammatory diseases (anti-IL-12/23 p40, anti-IL-17, anti-IL-1, anti-tumor necrosis factor, anti-Blys/B-cell activating factor belimumab, lenalidomide, bortezomib, tofacitinb (JAK1 and JAK2 inhibitor) among others. All these have been used in case reports or small case series of a variety of vasculitis.

Although performing clinical trials with all these drugs and disease variants is not feasible for short or medium-term, perhaps a consensus stratified and sequential approach, which also takes also in consideration heterogeneity and subtypes, would contribute to improvement in the care of refractory patients.

DISCLOSURES

All the authors declared no competing interests.

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